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Review article

Neonicotinoids: A critical assessment of the global research landscape of the most extensively used insecticide

Doris Klingelhöfer *, Markus Braun, Dörthe Brüggmann, David A. Groneberg

Institute of Occupational, Social and Environmental Medicine, Goethe University, Theodor-Stern-Kai 7, 60590, Frankfurt, Germany

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ABSTRACT

The broad-spectrum insecticides in the neonicotinoid group are the most widely used worldwide because of their widely recognized advantages in the mode of action. Therefore, their use is growing on a large scale and, moreover, is often used preventively without considering the ecological impact. Studies demonstrated harmful effects on non-target organisms, which in turn negatively impact biodiversity and thus food production. The dramatic decline of honey bee colonies, for example, could be linked to the use of neonicotinoids. Ecologically sustainable solutions to this conflict must be focused by scientific research. The question arose whether the global research efforts meet these requirements on a global scale. Therefore, this review article aimed to analyze the global research landscape on neonicotinoids under ecological, economic, and temporal aspects. To this end, key players and incentives for investigations in this research field are identified. The increase in publications over time is significant and shows a dynamic citation pattern. It indicates a comparatively high interest in current research, with ecological issues becoming more and more the focus of international research. It has been shown that national publication performance and funding are in line with global market interests, with the most publishing country being China. In addition, the elevated status quo of the scientific infrastructure in high-economy countries and their willingness to support research can be linked to national research output. Lower economies are sparsely involved in published studies. The research performance accumulates with a high North-South divide. Therefore, future research projects must have a sustainable focus and take regional requirements worldwide into account. This requires greater involvement of developing countries as the most economically dependent regions with enormously increasing consumption rates. Solutions must be found to ensure sustainable food production against a backdrop of already declining biodiversity due to the large-scale use of neonicotinoids.

1. Introduction

A group of insecticides known as neonicotinoids for their nerve-damaging effects are active substances and the world's fastest-growing and currently most widely used class against a broad spectrum of sucking and some chewing insects. They are used in arable farming or horticulture and in private households, as well as for veterinary applications such as the control of ticks or fleas in pets (Casida, 2018). Neonicotinoids are widely valued because of their presumed lower toxicity to non-target organism, humans and the environment compared to other insecticides such as organophosphates or carbamates, and their flexible application and systemic mode of action (Goulson, 2013). These advantages led to a global market share of 25% in 2014 and, thus, to an expansion into new cultivation areas (Thompson et al., 2020).

Abbreviations: CAS, Chinese Academy of Science; CAAS, Chinese Academy of Agricultural Sciences; CHL, Cited Half-Life; CNPq, National Council for Scientific and Technological Development (Brazil); CAPES, Council for Higher Education (Brazil); DEMP, Density Equalizing Map Projections; EC, European Commission; EFSA, European Food Safety Authority; EU, European Union; GDP, Gross Domestic Product; FAO, Food and Agriculture Organization of the United Nations; IPM, Integrated Pest Management; IRAC, Insecticide Resistance Action Committee; JMPR, Joint Meeting on Pesticide Residues; MIIT, Chinese Ministry of Industry and Information Technology; nACHRs, nicotinic acetylcholine receptors; NewQIS, New Quality and Quantity Indices in Science; NIH, National Institutes of Health (USA); NSERC, Science and Research Council of Canada; NSFC, National Natural Science Foundation; SCI, Science Citation Index; TFSP, International Task Force on Systemic Pesticides; R&D, Research & Development; USDA, US Department of Agriculture; US EPA, US Environmental Protection Agency; WIA, Worldwide Integrated Assessment of the Impact of Systemic Pesticides on Biodiversity; WHO, World Health Organization; WoS, Web of Science.

* Corresponding author.
E-mail addresses: klingelhoefer@med.uni-frankfurt.de (D. Klingelhöfer), m.braun@med.uni-frankfurt.de (M. Braun), prevention@uni-frankfurt.de (D. Brüggmann), occup-med@uni-frankfurt.de (D.A. Groneberg).

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Structurally, they are alike nicotine. (Tomizawa and Casida, 2005). They function systematically and are taken up, transported into the leaves, flowers and other parts throughout the plants. Ingested by insects, they bind irreversibly to nicotinic acetylcholine receptors (nACHRs). Neonicotinoids cannot be broken down by acetylcholine, which leads to nerve stimulation, paralysis and finally to the death of the insects. They are mainly used as seed treatment, but also as aerial, ground sprays, chemigations or injections (Simon-Delso et al., 2015). Although nACHRs are more frequently found and show a stronger interaction in insects, they are also existent in the peripheral and central nervous system of mammals. It is therefore estimated that neonicotinoids are five to ten times more selective for insects as for example organophosphates (Tomizawa and Casida, 2005).

However, their widespread use and the prophylactical application as seed coatings contradicts the established principles of integrated pest management (IPM), which is based on avoiding broad-spectrum pesticides when possible and announcing through monitoring when pesticide application is not avoidable (Goulson, 2013). Due to their systemic mode of action and their ubiquitous presence and high persistence in the environment, neonicotinoids pose a risk to the environment, wildlife, and human health (Thompson et al., 2020). Their half-live in soils varies widely, reaching almost 19 years for Clothianidin (U.S.EPA, 2010), and they are often found in ground water or surface water as even in tap water due to their water solubility (Van Dijk et al., 2013). Neonicotinoids are also frequently detected in food and pollen, as washing does not remove all residue (Chauzat et al., 2006; Chen et al., 2014; Kapoor et al., 2013). Thus, they also find their way to non-target organisms up to humans and there is evidence that the intensive use of neonicotinoids is associated with the decline of biodiversity (Goulson, 2013).

The regional mass mortality of bees has been shown to be linked to the large-scale use of neonicotinoids. In 2013, the European Food and Safety Authority (EFSA) declared neonicotinoids to be an unacceptably high risk to wild and honey bees (EFSA, 2018). A decrease of a broad variety of insects in areas with neonicotinoid usage could already be stated (Sanchez-Bayo and Wyckhuys, 2019). Consequently, the European Union (EU) restricted the use of the neonicotinoids Clothianidin, Imidacloprid, and Thiamethoxam in plant protection and seed treatment products. In 2018, these restrictions were backed up by extensive data collection, and all outdoor uses of the three products were banned. Due to the risk of endocrine disruption, the approval for the neonicotinoid Thiacloprid was not renewed in 2020 (EU, 2020). In 2019, the US Environmental Protection Agency (US EPA) canceled twelve neonicotinoid containing products (U.S.EPA, 2019). That same year, the Joint FAO/WHO (Food and Agriculture Organization of the United Nations/World Health Organization) Meeting on Pesticide Residues (JMPR) set the acceptable daily intake levels at 10–200 g/kg body weight for various neonicotinoids for a lifetime without appreciable health risk to health (Thompson et al., 2020). However, EPA assessed the risk from dietary ingestion to humans in the USA as not of concern because exposure is not estimated to exceed the proposed levels (U.S. EPA, 2017). Nevertheless, in 35% of all countries there is no pesticide legislation at all, so the three neonicotinoids in question are still the most used in the world (Rowe, 2019).

There are already numerous studies that demonstrate the contribution of nicotinoids to the devastating losses of pollinators, especially honey bees, but the effects on human health have hardly been researched until now (Thompson et al., 2020) although incidences suggest damaging effects for the nervous system and the brain (EFSA, 2013). Further research is therefore needed including on the cumulative effect of the metabolites (Bonmatin et al., 2015). Rural areas, in particular, should be in the focus of attention when assessing the pollution of drinking water (Thompson et al., 2020).

To assess whether global research meets the requirements of a balanced study regime, this study aimed to analyze the publication landscape on neonicotinoids. Scientists, stakeholders, and policy makers will benefit from the results by obtaining background information on trends, incentives, funding, and requirements of global research.

2. Methods

2.1. Methodological platform and data source

The present review article was conducted using the methodological approach and tool of the established bibliometric platform *New Quality and Quantity Indices in Science* (NewQIS) (Groneberg-Kloft et al., 2009), which was applied to a variety of scientific issues (Bruggmann et al., 2017; Quarcoo et al., 2015). The core collection of the online literature database Web of Science (WoS) serves as a standard data source. In addition to the metadata of the publication, it provides information about the citation numbers via its citation report and makes them available for analyses of quality measured as recognition in the scientific community.

2.2. Data collection

The elaborated search term was used in the title of the articles and searches for the generic term neonicotinoid* as well as the various terms combined with the Boolean operator “OR” and asterisks as placeholders for plural forms: “neonicotinoid* OR imidacloprid OR thiamethoxam OR clothianidin OR acetamiprid OR thiacloprid OR dinotefuran OR nitenpyram OR sulfoxaflor OR guadipyr OR huanyanglin OR paichongding OR Cycloxaprid OR imidaclothiz OR nithiazine”. The results were then filtered by the document type “Article” to include only original articles in the analysis database. No time limit was imposed, so the period under study extended from 1900 to the present. All integrated indices were included. The metadata of the retrieved entries were collected and stored in a MS Access database according to the tags contained for the different analysis parameters. Additional values have been retrieved from the World Bank (TheWorldBank, 2019a; TheWorldBank, 2019b) for socio-economic analyses, and from FAOStat for neonicotinoid-specific analyses (FAO, 2020; FAOStat, 2020). Here, insecticide consumption act as a proxy, as no valid figures for neonicotinoid use per country were available. In the case of China, the insecticide numbers were not provided, so the value was calculated based on the percentage of insecticides in pesticide use, which is 26% (CIRS, 2019).

2.3. Analyses and presentation

Based on the collected metadata, a quantitative and qualitative analysis was performed to determine the chronological and geographical patterns of publications on neonicotinoids. Incentives, trends, and regional interests were focused. For this purpose, the annual publication and citation figures, as well as the most frequently cited articles were identified. The performance of the publishing countries in the field of neonicotinoids was assessed using absolute and relative parameters. The relation of article numbers to socio-economic characteristics, such as total population (TheWorldBank, 2019b) and gross domestic product (GDP) (TheWorldBank, 2019a), and neonicotinoid-specific characteristics, such as insecticide consumption and the number of beehives, were applied to reflect the regional interest and to better assess countries’ publication efforts on neonicotinoids (FAOStat, 2020). Here, the insecticide use was taken as a proxy for neonicotinoid use as these values were not available for the publishing countries. For China, for which data on insecticide use were also not available, the average percentage of insecticides in pesticide use was applied. Average values of 20 years from 1999 to 2018 were calculated. Linear regression, determination of residuals, and correlation analyses were performed to show the association of the included parameters with the article numbers on neonicotinoids. Subject areas were analyzed to show the development of disciplines publishing on neonicotinoids, and cluster analyses

demonstrate the main research foci. For visualization of the foci clusters, the VOSviewer (van Eck and Waltman, 2010) was applied to show all keywords that are applied at least 70 times (threshold).

3. Results

In total, 4013 articles (n) on neonicotinoids could be identified by the applied search strategy.

The first article was published in 1991. The number of subsequent publications remained below 100 until 2008 and produced n = 111 articles for the first time this year.

Thereafter, the publication output developed more steeply up to the maximum number of n = 465 articles in 2019. Similarly, the number of citations showed an increasing trend until 2015, after which it decreased rapidly. The timeline shows some peaks corresponding to the publication years of the most frequently cited articles on neonicotinoids (Table 1).

Table 1
Most cited original articles on neonicotinoids, c = number of citations, IF = Impact Factor, PNAS = Proceedings of the National Academy of Science of the United States of America.

Authors	c	Title	Journal	IF
Whitehorn et al. UK, 2011	610	Neonicotinoid Pesticide Reduces Bumble Bee Colony Growth and Queen Production	Science	41.845
Simon-Delso et al., Netherlands, 2015	496	Systemic insecticides (neonicotinoids and fipronil): trends, uses, mode of action and metabolites	Environmental Science and Pollution Research	3.056
Rundlof et al. Sweden, 2015	411	Seed coating with a neonicotinoid insecticide negatively affects wild bees	Nature	42.778
Iwasa et al. USA, 2004	387	Mechanism for the differential toxicity of neonicotinoid insecticides in the honey bee, *Apis mellifera*	Crop Protection	2.381
Hallmann et al. Netherlands, 2014	357	Declines in insectivorous birds are associated with high neonicotinoid concentrations	Nature	42.778
Alaux et al. France, 2010	316	Interactions between Nosema microspores and a neonicotinoid weaken honeybees (*Apis mellifera*)	Environmental Microbiology	4.933
Di Prisco et al. Italy, 2010	311	Neonicotinoid clothianidin adversely affects insect immunity and promotes replication of a viral pathogen in honey bees	PNAS	9.412
Bai et al. UK, 1991	278	Actions of Imidacloprid and a Related Nitromethylene on Cholinergic Receptors of an Identified Insect Motor-Neuron	Pesticide Science	1.606
Horowitz et al. Israel, 2005	277	Biotypes B and Q of Bemisia tabaci and their relevance to neonicotinoid and pyriproxyfen resistance	Archives of Insect Biochemistry and Physiology	1.563
Liu et al. China, 2005	269	A nicotinic acetylcholine receptor mutation conferring target-site resistance to imidacloprid in Nilaparvata lugens (brown planthopper)	PNAS	9.412

However, of the ten most cited articles on neonicotinoids, five are actually reviews (Bonmatin et al., 2015; Elbert et al., 2008; Jeschke and Nauen, 2008; Jeschke et al., 2011; Nauen and Denholm, 2005), although WoS categorizes them as original articles. Due to the fact that reviews are generally quoted more often, it is explainable that these publications occupy a high position in our ranking. We tend to exclude them from the table for reasons of comparison and instead list the following original articles, although the reviews contributed to the peaks in the timeline of citation numbers as well.

The comparison with the total number of articles listed in the Science Citation Index Expanded (SCIE) of WoS shows that the number of articles on neonicotinoids follows a steeper slope, which means that the publication output on neonicotinoids has increased relatively more than in biomedical science as a whole, and also that this increase shows a steady trend with higher rates in recent years. (Fig. 1B).

3.1. Research foci

The evaluation of the occurrence of keywords (threshold 70 occurrences) resulted in four main thematic clusters (Fig. 2). The most frequently used keyword was the first developed neonicotinoid herbicide “Imidacloprid”. It was assigned to the cluster covering entomological issues. Other keywords that belonging to this cluster refer to the mode of action of neonicotinoids in target organisms, the different insect species, and their gradually developing resistance to the toxicity of neonicotinoids. The second cluster deals with residues of neonicotinoids in food and their detection methods. This cluster forms the basis for the definition of limit values and maximum daily intake amounts for the regulatory authorities. The third main cluster focuses on the toxic effect on non-target organisms, especially in bees. The most commonly used keyword in this cluster is “Clothianidin”, a neonicotinoid that is blamed for bee mortality in many countries and has therefore often been banned.

The analysis of the research foci over time showed that of the two most frequently assigned subject areas in the WoS categories, “Entomology” decreased in relative terms from 45.71% in the early 1990s to 16.29%, while “Environmental Science & Ecology” increased from 2.86% in the early 1990s to 25.82%. These opposing trends can also be observed for the two areas “Food Science & Technology” (declining) and “Toxicology” (increasing). These courses are supported by the evaluation of the chronological sequence of the occurrences of keywords (Fig. 2B). The citation analysis of the keywords used showed that the topics related to the toxicity of metabolites to bees and insecticide resistance received the most attention (Fig. 2C).

3.2. Geographical patterns

From the database, which contains a total of 4013 articles on neonicotinoids, most of them, n = 3986 (99.33%), could be assigned to at least one country of origin. In the metadata, the country of origin was missing in only n = 27 articles.

China has written the most articles on neonicotinoids with n = 1007, closely followed by the USA (n = 906). By a larger margin, Germany ranked third (n = 280), followed by Japan (n = 264), and India (n = 250). Other leading positions were mainly held by high-income European countries, Canada, and Australia. Nevertheless, lower economies also ranked among the top 20, with Brazil contributing n = 155 articles, and Egypt and Pakistan each writing more than n = 80 articles (Fig. 3A). The most international collaborations took place between the USA and China (n = 85), followed by Germany and the UK (n = 46).

However, the proportions of the countries changed over time (Fig. 3B). At the beginning of the 1990s, the USA was the leading country among the top 10 with a share of 39.29%. At the end of the

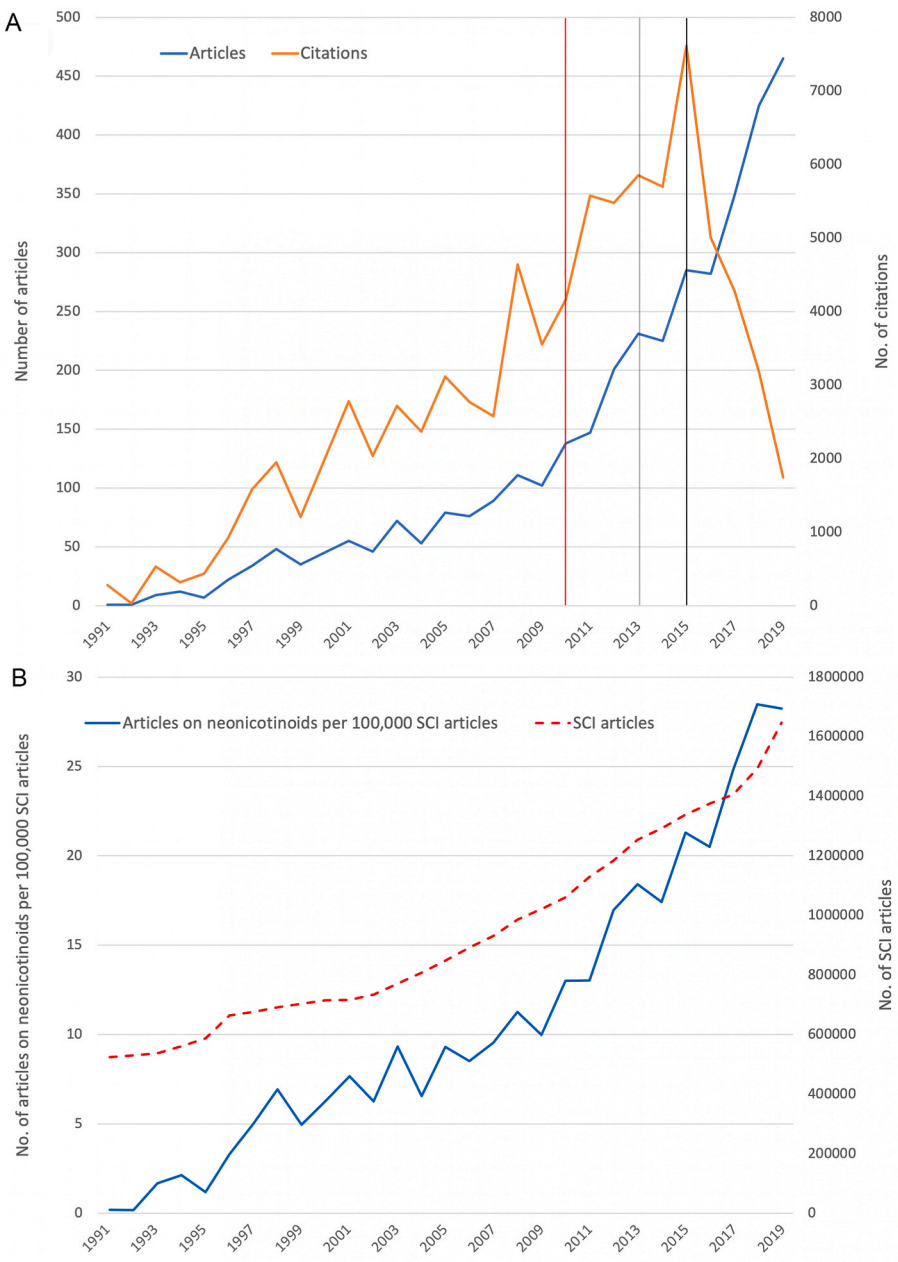

Fig. 1. Chronological time line from 1991 until 2019. A) Development of article and citation numbers. Red line: cited half-life of life sciences, gray line: cited half-life of biomedical sciences, black line: cited half-life of neonicotinoid research, B) Development of the number of articles per 100,000 articles listed in the Science Citation Index Expanded (SCI) and number of SCI articles. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

1990s, it was able to further expand its share. With China's incipient interest in neonicotinoid research at the beginning of the new millennium, the share of US articles began to decline. As a result, China overtook the USA in the period from 2011 to 2015, a position that has been consolidated in the last evaluation period, in which China's share was clearly the highest with 35.16%. Japan's share, initially in third place, decreased considerably over time, while the share of Germany remained more or less at the same level. Over time, Brazil came to the fore as an upper-middle-income economy and was able to position itself among the leading ten countries publishing on neonicotinoids.

The evaluation of the citation numbers of the publishing countries shows a similar pattern with a differing ranking (Fig. 4A). Here the USA dominated the ranking clearly with (c = 21,284). China, the country with the largest number of articles, followed at some distance (c = 14,517). Germany was in third place (c = 11,631), followed by the UK (c = 11,393), and France (c = 7311). Brazil also belongs to the top 20 (c = 1897). Egypt (c = 854) and Pakistan (c = 714) could at least position themselves among the top 30 in terms of the number of citations. Looking at the average citation rate (cr) of countries with at least n = 30 articles on neonicotinoids (threshold), the global landscape varies considerably. The leading country in this respect was the Netherlands (cr = 87.5), followed by Switzerland (cr = 54), the UK (cr = 48.28), Germany (cr = 41.54), and France (cr = 40.17). The most publishing countries USA (cr = 23.49, rank 24) and China (cr = 14.42, rank 39) were thrown back. The much-publishing weaker economies of Egypt (cr = 10.41) and Pakistan (cr = 8.81) were ranked far behind in the 50s ranks (Fig. 4B).

3.3. Socio-economic parameters

Particularly noteworthy in the calculation of ratios based on socio-economic figures for countries with at least 30 articles on neonicotinoids (threshold value) are Switzerland, Serbia, Canada and Greece. Switzerland is the leader in terms of the ratio of articles to the

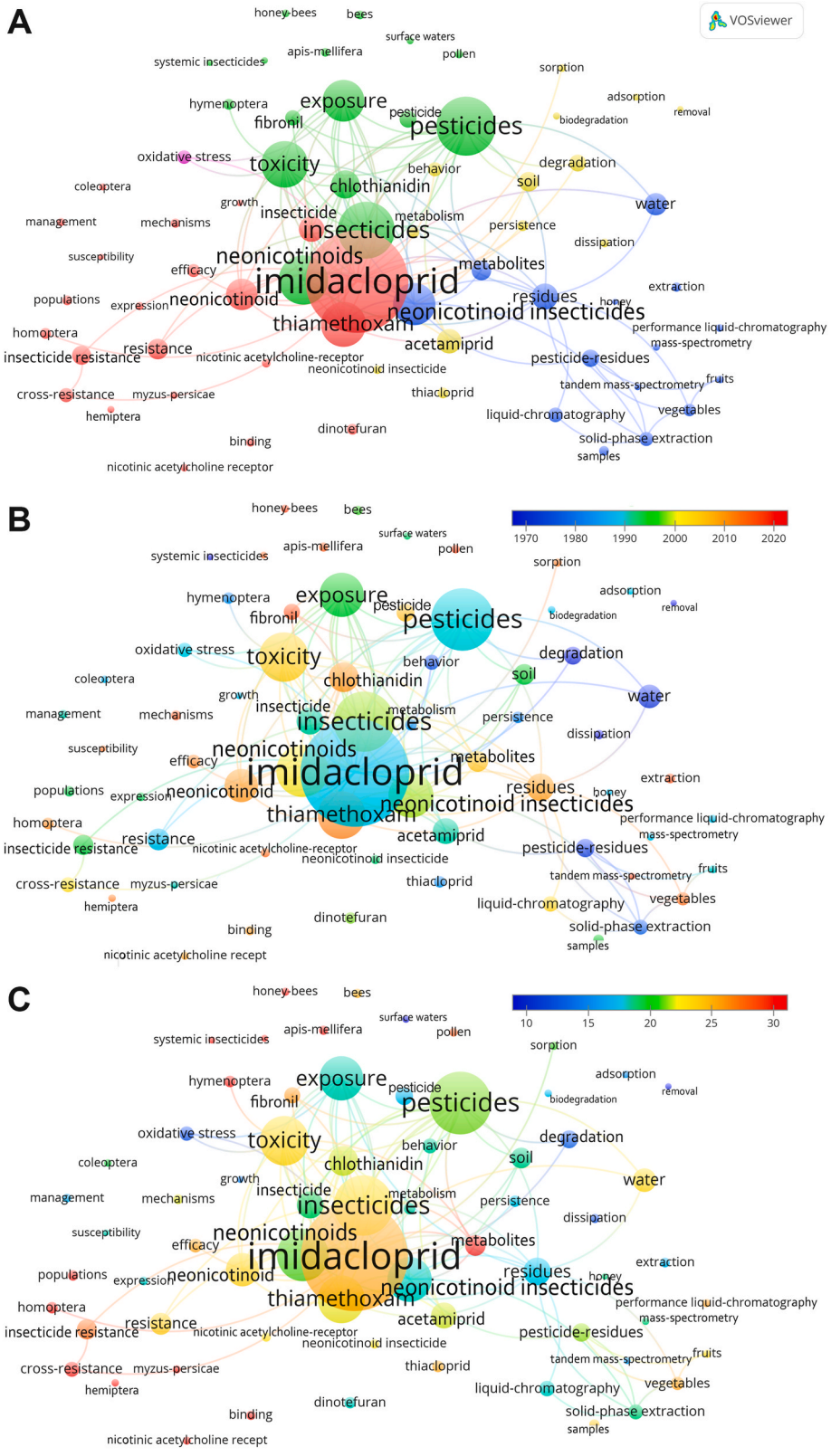

Fig. 2. Author keyword analysis (threshold: 70 occurrences). A) Keyword cluster. Main cluster: red – entomology, blue - detection methods of neonicotinoid residues in food, green – toxicity, especially to honey bees. Subcluster: yellow: environmental persistence, magenta: effects on human health. B) Timeline of keywords. C) Citation frequency of keywords. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

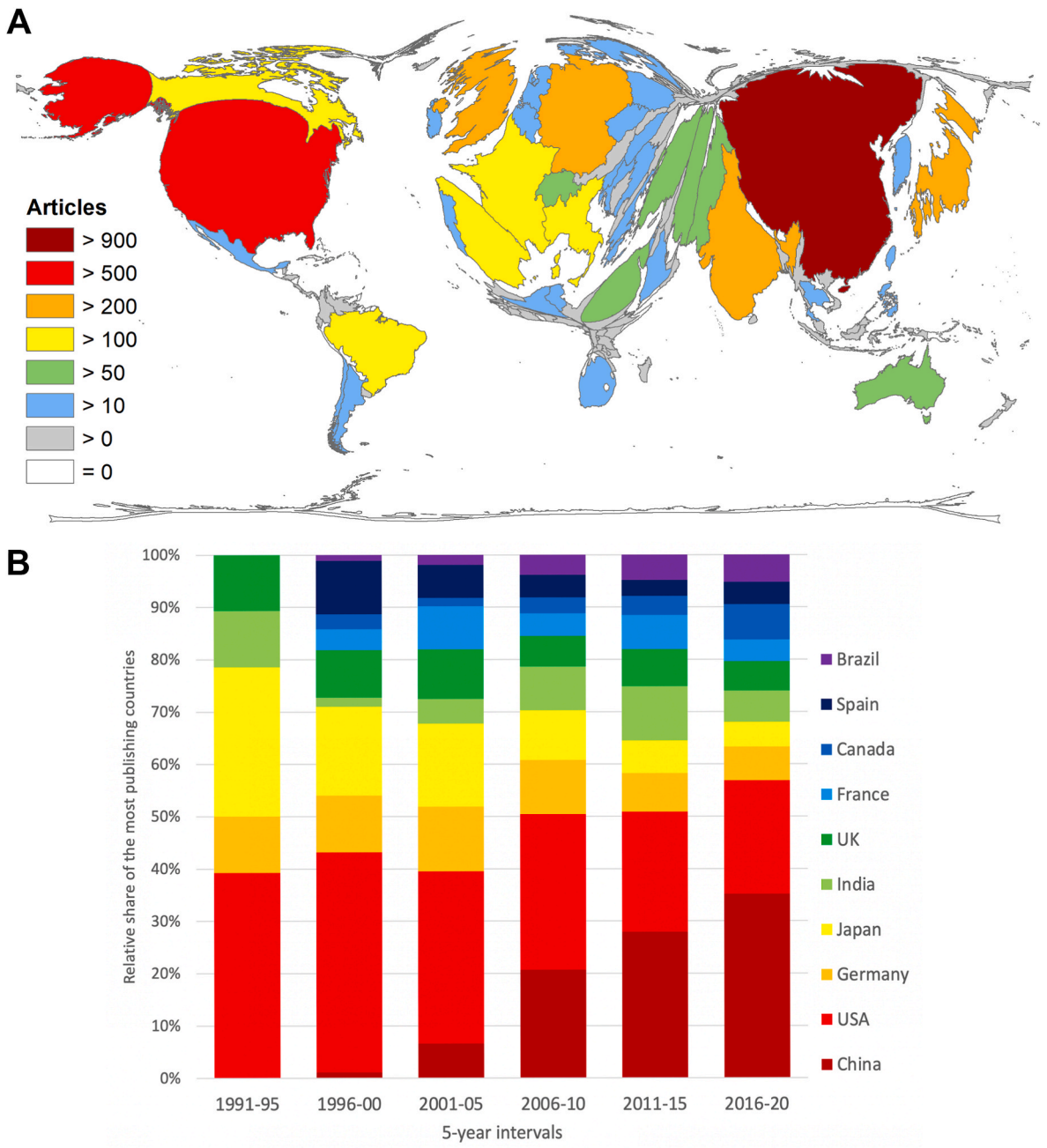

Fig. 3. Countries' performances. A) Number of articles per country. B) Relative share of articles of the most publishing countries in 5-year intervals.

population in million inhabitants (R_{POP}) and Serbia in terms of the ratio of articles to economic power measured by gross domestic product (GDP) in 1000 billion US dollars (R_{GDP}) The USA and especially China are falling behind in terms of socio-economic indicators (Table 2).

3.4. Most publishing institutions

Looking at the institutions with more than 30 articles on neonicotinoids (Table 3) the most publishing countries were also represented. Mainly Universities from China and the USA belong to these top 20, but Japanese, British and Spanish Universities were also listed. The most publishing institution is the University of California (USA) with n = 141 articles on neonicotinoids. In addition, national research institutes of China, France and India frequently published on neonicotinoids. Bayer, as one of the main manufacturers of neonicotinoids is listed with its German and US companies. The only institution that does not have its headquarters in a country listed in the top 10 was the University Novi Sad, which published almost all Serbian articles.

3.5. Global funding on neonicotinoid research

A total of 5083 grants (g) for n = 3824 articles neonicotinoid research from 74 countries could be identified with the applied search strategy. Of these, g = 2812 were financed by national governments of 64 countries. The other ten countries financed neonicotinoid research through university grants. Provincial governments participated with g = 1009 grants and cities with g = 31, most of which were Chinese municipalities. Intergovernmental funds provided g = 160 grants, with the EU contributing g = 111 grants. Private companies financed the neonicotinoid articles with g = 256 grants, with Bayer Corp. being the main donor (g = 114). Universities granted financial support for g = 546 (US universities g = 146). The remaining g = 251 funds were financed

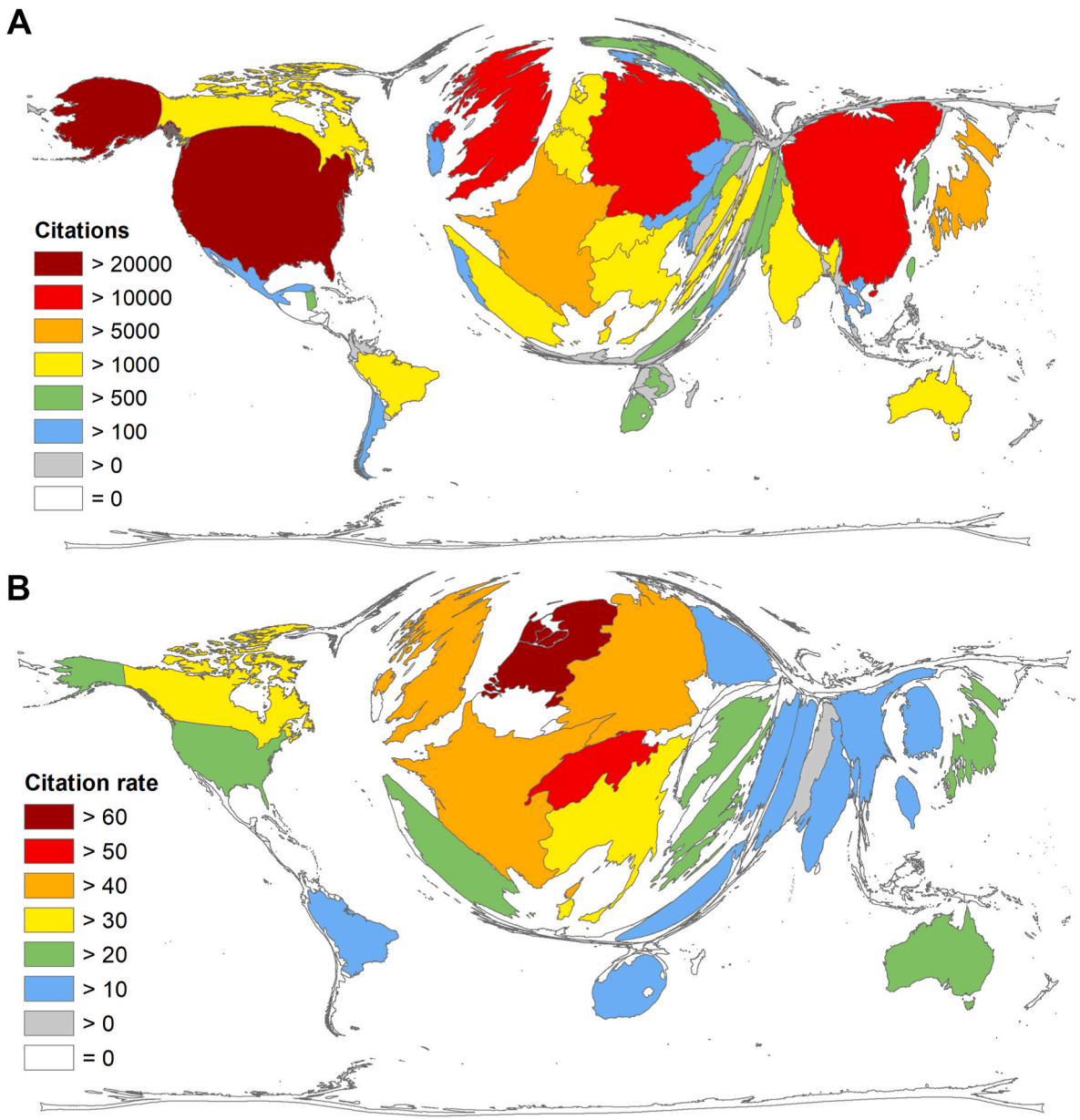

Fig. 4. Citation parameters of publishing countries with at least 30 articles on neonicotinoids (threshold). A) Number of citations. B) Average citation rate (number of citations/number of articles).

by research institutes, foundations, societies, non-profit organizations, farmer's associations, as well as animal and nature conversation organizations, where the protection of bees was a particular priority.

By far the most grants came from China (g = 2063), followed by the USA (g = 776), Canada (g = 243), Germany (g = 199), and UK as well as Brazil (each g = 194). In relation to the number of articles, China achieved the highest value with 2,23 grants per article, followed by Canada (1.49 grants per article), Brazil (1.28 grants per article), Spain (1 grant per article), and the USA (0.89 grants per article) (Fig. 5A).

The correlation between the number of articles and the number of grants per country was highly significant with a Spearman r = 0.843. The linear regression showed a coefficient of determination of $r^2 = 0.79$ (Fig. 5B).

China exhibited the largest deviation from the regression line with the largest gap in the positive range. In contrast, the USA showed the largest deviations in the more negative range. Other countries with positive deviations were Canada, Argentina and Thailand (Fig. 6).

The comparison of the individual programs or institutions also shows Chinese donors in leading positions with the National Natural Science Foundation (NSFC) of China leading the way with g = 488 grants for neonicotinoid research. The U.S. Department of Agriculture (USDA) supported g = 166 grants, followed by the neonicotinoids manufacturing and development company Bayer Corp. with g = 114 grants. In addition to Chinese and US donors, Brazilian and Canadian donors were also among the top 10, but the US National Institutes of Health (NIH) led by far in the average citation frequency of funded articles (cr = 41.44), while the NSFC dropped considerably (cr = 7.42) (Fig. 6).

3.6. National market parameters

Two parameters were selected for the analysis of market characteristics of countries publishing on neonicotinoids. First, the average use of insecticides per country reflects the national interest in neonicotinoid research according to the average application amount on conservatively cultivated farmland.

Table 2
Ranking of countries (threshold = 30 articles) according to socio-economic figures, n = number of articles, R_{POP} = n/population in mill., R_{GDP} = n/Gross Domestic Product (GDP) in 1000 bn US dollars (USD), HI = high-income countries, UMI = upper-middle-income countries, LMI = lower-middle-income countries, sorted by R_{POP}.

Country	N	Population in mill.	R_{POP}	Rank R_{POP}	GDP in 1000 bn USD	R_{GDP}	Rank R_{GDP}
Switzerland	63	8.18	7.70	HI 1	0.49	127.45	HI 2
Serbia	45	7.14	6.30	UMI 1	0.10	443.35	UMI 1
Canada	163	35.36	4.61	HI 2	1.67	97.37	HI 3
Greece	49	10.77	4.55	HI 3	0.29	168.67	HI 1
UK	229	64.43	3.55	HI 4	2.79	82.14	HI 5
Germany	278	80.72	3.44	HI 5	3.98	69.87	HI 6
Australia	79	22.99	3.44	HI 6	1.19	66.44	HI 7
Spain	153	48.56	3.15	HI 7	1.69	90.53	HI 4
USA	878	324.00	2.71	HI 8	18.56	47.31	HI 12
France	178	66.84	2.66	HI 9	2.74	65.03	HI 8
Netherlands	43	17.02	2.53	HI 10	0.87	49.66	HI 10
Japan	263	126.70	2.08	HI 11	4.93	53.33	HI 9
Italy	109	62.01	1.76	HI 12	2.22	49.08	HI 11
Taiwan	30	23.46	1.28	HI 13	1.13	26.67	HI 14
Turkey	93	80.27	1.16	UMI 2	1.67	55.69	UMI 3
Poland	37	38.52	0.96	HI 14	1.05	35.17	HI 13
South Africa	49	54.30	0.90	UMI 3	0.74	66.55	UMI 2
South Korea	45	50.92	0.88	HI 15	1.93	23.33	HI 15
Iran	72	82.80	0.87	UMI 4	1.46	49.35	UMI 4
Egypt	79	94.67	0.83	LMI 1	1.11	71.49	LMI 2
Brazil	152	205.82	0.74	UMI 5	3.14	48.48	UMI 5
China	925	1373.54	0.67	UMI 6	21.27	43.49	UMI 7
Pakistan	79	202.00	0.39	LMI 2	0.99	79.94	LMI 1
India	250	1266.88	0.20	LMI 3	8.72	28.67	LMI 3

Table 3
Most publishing institutions.

Institution	Country	Articles	Citations	Citation rate
University of California	USA	141	4748	33.67
Bayer AG	Germany	138	6988	50.64
Chinese Academy of Agricultural Sciences	China	111	1606	14.47
Nanjing Agricultural University	China	86	2124	24.70
China Agricultural University	China	86	1293	15.03
U.S. Department of Agriculture	USA	73	2055	28.15
East China University of Science and Technology	China	60	1095	18.25
Bayer Crop Science	USA	52	1144	22.00
French National Institute for Agricultural Research	France	51	3366	66.00
Zhejiang University	China	51	1027	20.14
Chinese Academy of Science	China	45	475	10.56
Gifu University	Japan	41	955	23.29
Shandong Agricultural University	China	40	638	15.95
Indian Agricultural Research Institute	India	40	832	20.80
Rothamsted Research	UK	39	2768	70.97
University Novi Sad	Serbia	37	979	26.46
Michigan State University	USA	34	809	23.79
University of Almeria	Spain	32	1148	35.88
University of London	UK	32	1129	35.28
North Carolina State University	USA	31	752	24.26

Second, the number of beehives per country is also related to the interest in neonicotinoid research for bee protection and the impact of residues in honey that are of interest for beekeepers and integrated agriculture. The interests of the various farmers' groups in the publishing countries are thus characterized by opposing arguments, which are also mirrored in the global research landscape.

Both parameters correlated significantly with the number of articles on neonicotinoids (insecticides: Spearman r = 0.665, beehives: Spearman r = 0.580).

The coefficient of determination of the linear regression was equally significant (insecticides: $r^2 = 0.60$, beehives: $r^2 = 0.317$), although the approximation to the regression line was less in terms of the regression of the number of articles and the number of hives. Looking at the residuals showing the positive or negative deviation from the regression line of the countries with at least 20 articles on neonicotinoids (threshold), showed a different picture when comparing the two parameters (Fig. 7).

When looking at the number of articles and their association to both parameters, China showed a positive deviation from the regression line, while the USA revealed a negative deviation, i.e., China elaborated relatively more articles and the USA relatively less articles related to the use of insecticides and to the number of hives. The majority of the other publishing European countries also displayed a negative, albeit smaller deviation in both parameters. India, Spain, Turkey, Iran, Greece, South Korea, and Poland showed a clear positive deviation in the number of beehives and a negative deviation in the amount of insecticide used. Argentina, which also had a positive deviation in beehives, almost touched the regression line regarding the use of insecticides with only a small positive deviation.

4. Discussion

4.1. Chronological development of neonicotinoid publishing

The development of the article numbers on neonicotinoids showed a steadily rising curve, similar to other scientific topics (Quarcoo et al., 2015)' (Bruggmann et al., 2017). Neonicotinoid research started with the first article in 1991 and then increased up to about n = 100 articles in 2009. From then on, the slope of the curve is steeper and shows a larger annual increase in publications. The first study is a British-German collaboration between the zoological faculties of the universities of Cambridge (UK) and Stuttgart-Hohenheim (Germany) and the German company Bayer AG, which developed the first commercialized neonicotinoid called Imidacloprid. Its mode of action on a motor neuron of an insect is explained in this article (Bai et al., 1991). With c = 278 citations up to the time of evaluation, it was listed among the most cited articles. The analysis of keywords revealed that the term Imidacloprid was the most commonly used term, but it was mainly occurring in the early years of neonicotinoid publication. Previously, Nithiazin was developed, which can be called a prototype of neonicotinoids, but it was never on the market due to its low photochemical stability. Without its potential

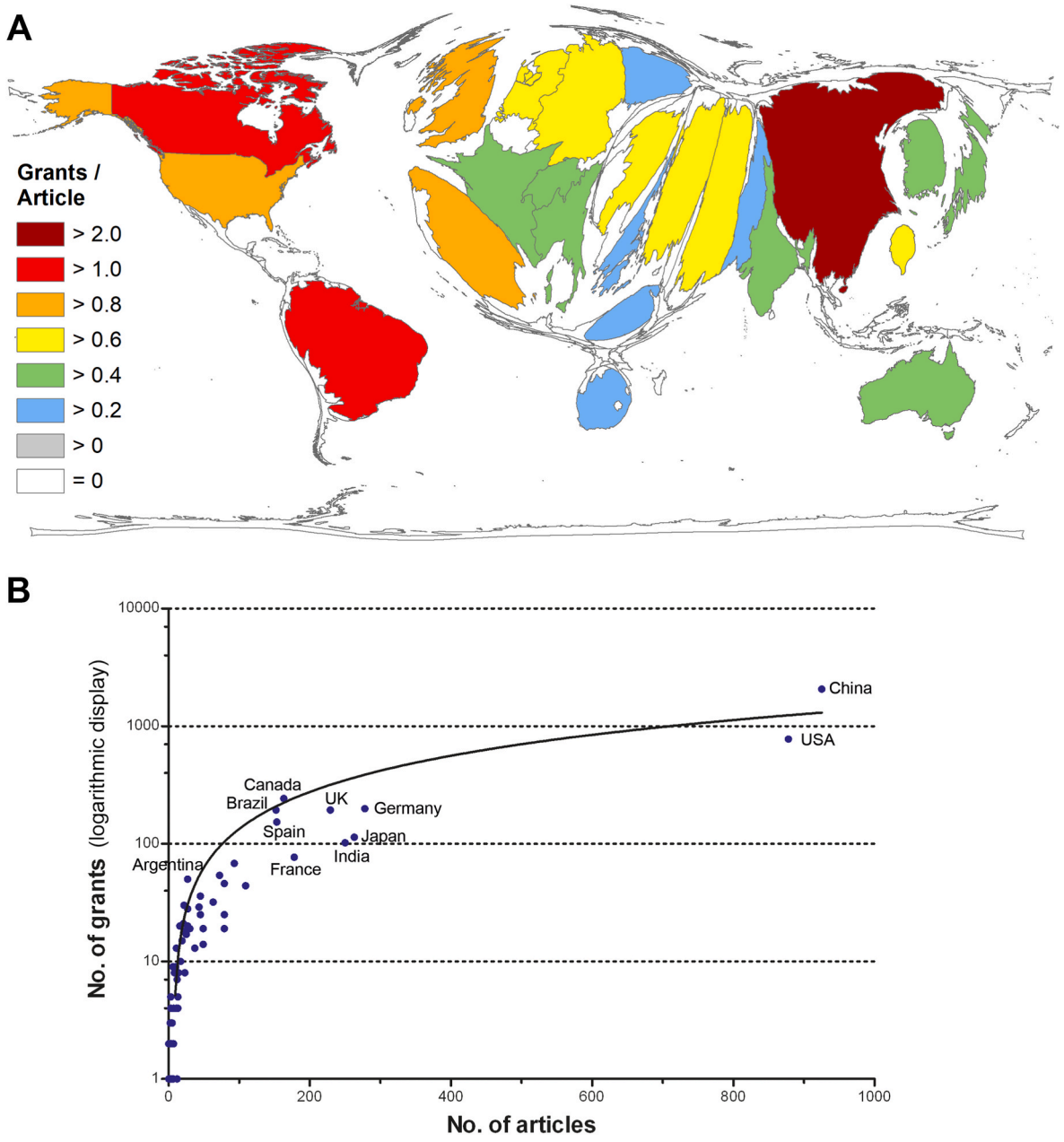

Fig. 5. Grants on neonicotinoid research. A) Ratio of grants to articles per country (threshold 30 articles). B) Linear regression of the number of grants and the number of articles ($r^2 = 0.79$), logarithmic display of y-axis, display: number of grants >0.

use as a systemic herbicide, interest from the scientific community was low and thus began to develop later when Imidacloprid came on the market. N = 1664 articles could be directly associated with Imidacloprid due to the presence of the term in the title of the articles. Most research efforts on Imidacloprid were of US-American origin, mostly with an entomological focus.

The development of the average annual citation numbers showed some minor or major peaks over time. The year with the most frequently cited articles so far was 2015, when two of the most cited articles were published (Rundlof et al., 2015; Simon-Delso et al., 2015). However, the renewed decline thereafter is not related to a significant decrease in scientific interest in neonicotinoids, but is due to a bibliometric effect related to the time of publication. This effect refers to the time required to reach half of the expected citation frequency and, therefore, is called Cited Half-life (CHL). In the life sciences, CHL is estimated to be up to ten years, while biomedical articles reached this point faster with a CHL of approximately eight years. This points to a rather static citation behavior of the life sciences, which is not confirmed by global neonicotinoid research. In contrast, it shows a shorter CHL of five years, demonstrating the extremely strong interest in the new findings, which are even more dynamic as the biomedical citation behavior. While the dynamics of Glyphosate, a highly controversial herbicide, showed a CHL of ten years appropriate for life sciences (Klingelhofer et al., 2020).

Another citation peak that is not related to the publication years of the most cited articles, is the year 2008, in which the number of articles also increased relatively more. This was three years after the first neonicotinoid was approved in the EU (EC, 2020). In this year (2015), the first global workshop on stewardship of neonicotinoid insecticides took place with participants of the public and the private sectors with the aim to react to the increasing resistance of various insects towards neonicotinoids. Here, leading companies in neonicotinoid generation as Bayer Crop Science (Germany) and Syngenta (USA) were in charge. The

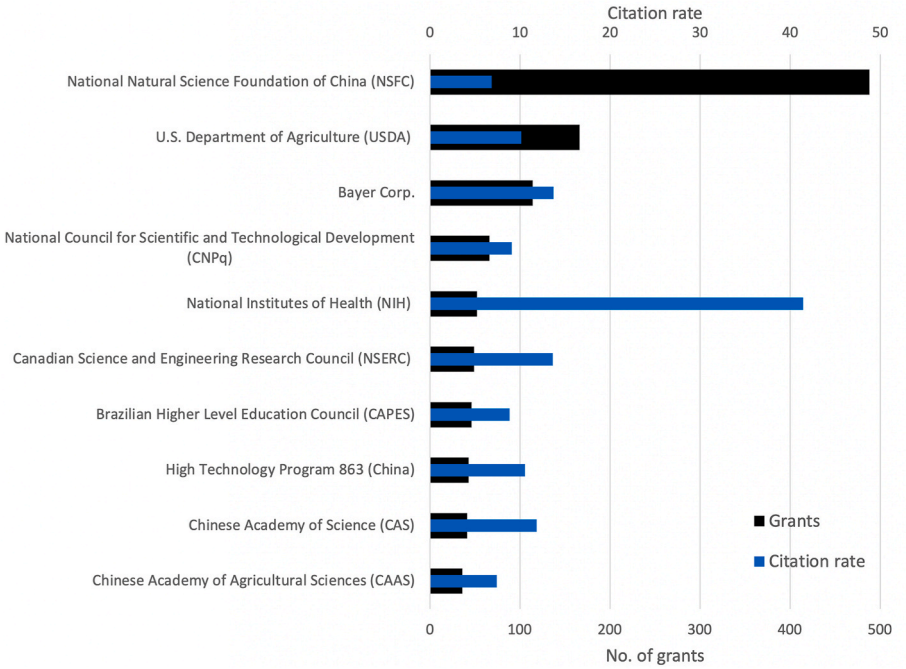

Fig. 6. Top ten funding programs, institutions, or companies.

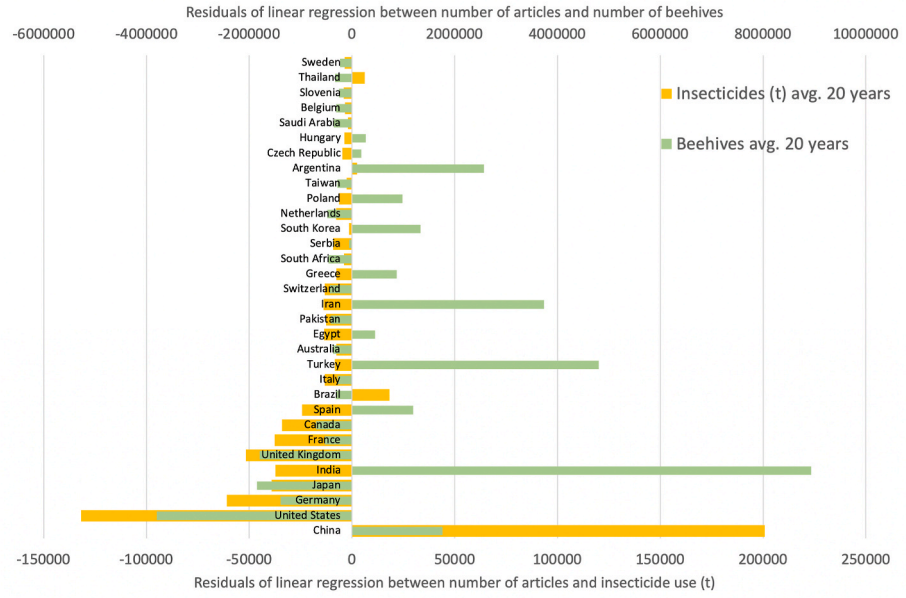

Fig. 7. Residuals of the linear regression between the number of articles and the use of insecticides (t) and the number of articles and the number of beehives in countries with at least 20 articles on neonicotinoids. Average values from 1999 to 2018 (FAO, 2020).

consensus among all participants was the urgent need to publicly emphasize the role of neonicotinoids in the food supply. In the same year, the IRAC (Insecticide Resistance Action Committee) Guidelines for Resistance Management of Neonicotinoids were established.

Hence, the interests of the different parties are crucial especially in this time and their recognition of research results therewith not objective but biased (Maxim and van der Sluijs, 2010) to which also scientists are prone (Cresswell, 2014).

From 2013 onwards, European farmers are prohibited to use the three neonicotinoids Imidacloprid, Clothianidin, and Thiamethoxam for seed treatment for due to a decision of the European Commission (EC) to restrict this mode of use on those crops attractive to bees (Noleppa, 2017). This was based on an evaluation of the European Food Safety Authority (EFSA). For these neonicotinoids, further information was requested for the applications that were still allowed (EC, 2020). Two years later, a revision of the scientific status should take place. For this, a lot of studies were financed and carried out with the focus on adverse effects on bee populations leading to a surpassing of the environmental focus of research that was settling as a leading area. The overall recognition of the studies published earlier shows the interest in these findings based on the controversial led debate. This is underscored by the significantly increased annual proportion of neonicotinoid articles relative to all SCI articles.

It was until five years later, in 2018, that an almost complete outdoor

ban on the three neonicotinoids in question was issued by the EC to protect bees. As a result, the approvals expired in 2019 respectively in 2020 (EC, 2020). Nevertheless, these bans were often bypassed by applications for "emergency" authorizations often held by the manufacturers themselves (Dowler and Sandler Clarke, 2020).

To date, there are no other national bans on the use of neonicotinoids. The US EPA only proposes restrictions to limit the exposure of bees (U.S.EPA, 2020), and the Canadian provinces Ontario and Quebec have banned all uses unless they are proven to be justified (Zhang et al., 2018), and with this wording also paving ways for eventual approvals.

4.2. Geographical patterns of neonicotinoid publishing

Although EU countries are the only nations to restrict the use of neonicotinoids by law, their share of research on neonicotinoids is not increasing as much as that of other countries. This indicates the increased interest in the environmental focus of neonicotinoid research worldwide, as these are the topics currently receiving the most attention from the scientific community. In Canada, where bans also were issued in some provinces, the share in neonicotinoid publications increased slightly over time. The largest increase in publication numbers has been demonstrated for China, which overtook the USA as the world leader in neonicotinoid research in the mid-2010s and continues to maintain this position to this day.

As a large traditional agricultural country, China has intensively expanded the use of pesticides over the past decade. It is now the world's largest producer of pesticides. Accordingly, international trade has also increased significantly, so that China now plays an important role in the global supply of neonicotinoids. Of the total amount of pesticides, insecticides account for 44%, and of them, the neonicotinoid market is the largest. The seed treatment market in particular is expected to grow by 14,2% in China over the next years (Ciston, 2019). This explains the large number of governmental programs that support neonicotinoid research (Shao et al., 2013). As our results show, China's NSFC is the most funding institution worldwide and CAS and CAAS are in the top ten. Governmental programs as the High Technology Program 863 of China are also among the leading sources of support. They are primarily focused on developing novel neonicotinoids with better resistance patterns, as the Chinese Ministry of Industry and Information Technology (MIIT) has set production restrictions on existing neonicotinoids due to their current exorbitant use rates and resulting resistance development (Thompson et al., 2020). In this way, China achieved mutual benefit for the neonicotinoid producers and also for the farmers through increased efficiency in crop protection (Shao et al., 2013). In addition, the Chinese government's fundamental desire to support research by increasing spending on R&D also contributed to the growth in neonicotinoid research (OECD, 2019).

Interest in neonicotinoid research by the second most publishing country, the USA also appears to be driven primarily by economic interests. In the USA, there has been a spatial concentration of agricultural land with a resulting increase in the use of agrochemicals (Crossley et al., 2021). It is the largest seed treatment market, where neonicotinoids were holding a share of 80% in 2008. Consumption increased, especially from 2003 onwards. It is estimated that this market will grow at 10 bn USD per year (Ciston, 2019; Thompson et al., 2020). The USDA ranked second, and the NIH were also in the top ten organizations with the most grants, but is only 5th in terms of grants per article ratio. Furthermore, the USA shows a relatively more negative ratio of neonicotinoid articles and insecticide usage than China, which has the best ratio in this study.

The order of the most publishing countries continued with Germany and Japan on position three and four. As countries of origin of the developers of neonicotinoid insecticides, these positions seem to be conditioned by the interests involved. The seven most common neonicotinoids are Imidacloprid introduced by Bayer CropScience (Germany) in 1991, Nitenpyram and Acetamiprid in 1995 by Sumitomo Chemical Takeda Agro Co. (Japan), Thiamethoxam in 1998 by Nippon Soda (Japan), Clothianidin (Sumitomo Chemical Takeda Agro Co./Bayer CropScience), and Thiacloprid (Bayer CropScience) in 2001, and Dinotefuran in 2002 by Mitsui Chemicals (Japan) (Jeschke et al., 2011). However, in terms of the level of funding support, measured in grants per article, Germany was only 10th and Japan only 16th, although Bayer AG (Germany) was the second most publishing and the third most funding institution of this study.

In terms of the ratio of grants per article, other countries positioned themselves in the top ranks. China was followed by Canada and Brazil, which also reflects their positions among the most publishing countries. Thus, a correlation between the market volume of the countries and the publication interest could be observed. Additionally, a significant relationship was found between publication performance on neonicotinoids and insecticide use per country.

To protect bee populations, Canada stopped using neonicotinoids on crops attractive for bees, such as orchard trees, in 2019 and has implemented mitigation measures as early as 2012, which have already led to a decrease in bee incidents (Canada, 2020). Still, only the governments of some Canadian provinces have enacted bans on neonicotinoid use so far, but review decisions are pending for 2021. Canada is therefore pushing research on neonicotinoid levels across the country. In the present study, the Science and Research Council of Canada (NSERC) ranked 6th among funding agencies. With $n = 163$ articles on neonicotinoids, Canada ranks 8th in national publication performance but has not increased its share over time. In terms of socio-economic parameters, however, Canada ranks among the top 5 with Switzerland, Serbia, and Greece.

Brazil, which ranked third in terms of grants per article, supported neonicotinoid research mainly through the government institutions, such as the National Council for Scientific and Technological Development (CNPq) and the Council for Higher Education (CAPES), both of which ranked in the top ten. Its share of the publication count has steadily increased over time, focusing mainly on environmental sciences. Brazil is the South-American country that uses the most pesticides and ranks third in the world, resulting in the highest honey bee colonies losses (Castilhos et al., 2019).

Switzerland, which ranked first and third in socio-economic parameters, had 63 articles on neonicotinoids that received 3402 citations, also ranking at the top of citation rates along with the Netherlands. Utrecht University (Netherlands) and the University of Neuchâtel (Switzerland) participated in the *International Task Force on Systemic Pesticides* (TFSP) research group, which aims to provide an unbiased scientific of the effects of systemic pesticides on biodiversity and ecosystems and related concerns (TFSP, 2020). The multidisciplinary team of TFSP contributed to the *Worldwide Integrated Assessment of the Impact of Systemic Pesticides on Biodiversity* (WIA) that is the largest evaluation of neonicotinoids to date. It comprises 1121 peer-reviewed studies from the last five years and, thus, certainly contributed to the increasing number of publications on neonicotinoids over time.

In terms of socio-economic analyses, Serbia also took leading positions. The Serbian researchers were specialized in the determination of neonicotinoids. Most of their articles were thus assigned to the research field of chemistry and originated from the University of Novi Sad. Their publication period began only in 2011, with a rapid maximum in 2012 and a decline shortly thereafter, so Serbia is unlikely to play a prominent role in future neonicotinoid research.

Another parameter included in the analyses was the linkage of articles on neonicotinoids to the number of hives per country to assess the countries' interest in bee conservation versus neonicotinoid market interests. A correlation could also be calculated for this relationship. Besides China, India, Turkey, and Iran as countries with the highest number of hives showed the largest positive deviation from the regression line.

All in all, the market interests of consumers and producers of neonicotinoids, as well as the agricultural interests of both sides, arable

farmers and beekeepers, seem to play a major role in the countries' involvement in neonicotinoid research. Whereby the economic power of the countries and, thus, their possibilities to finance research projects have a great influence on the absolute publication figures, so that lower economies hardly participate in the research output, although their consumption is among the highest worldwide with high annual growth rates (FAO, 2020). Therefore, the global interest in research that is independent of market interests is just as important as the involvement and support of infrastructurally disadvantaged regions to meet the needs and burdens worldwide.

Although environmental research has increased relatively over time and the observed bee mortality and biodiversity decline can also be attributed to the enormous use of neonicotinoids, the new approaches are hardly noticeable in practice, considering the still widespread use for prophylactic pest control around the world.

5. Conclusions

Despite scientific evidence of negative impacts on the biosphere and the achievement of critical resistance levels in insects, most pest management programs continue to rely on the use of neonicotinoids. In contrast, the safety of food production should be weighed against ecological damage such as biodiversity loss, and inclusive production should be encouraged. For global production, balance must be found that takes both aspects into account and identifies the best possible solutions for sustainable food production at the regional level.

Many scientifically sound studies already show the negative effects of the intensive use of neonicotinoids. The extreme dynamics of recent citation numbers show the continued high interest in the research results. Although ecological emphases are increasing in the process, much of the research is conducted from an economic and production perspective, demonstrating the importance of the main producer and consumer states.

It is therefore necessary to ensure that concerns about the intensive use of neonicotinoids are increasingly addressed scientifically worldwide. This should increasingly involve countries with limited scientific infrastructure, independent of economic interests, so that regional producers can benefit. This requires international research synergies to provide unbiased and independent research results also for regulators, policy makers and research funders.

Author contribution

Doris Klingelhöfer: Conceptualization, Data curation; Investigation; Methodology; Formal analysis; Supervision; Visualization; Writing – original draft; Writing – review & editing; Markus Braun: Resources; Validation; Visualization; Writing – review & editing; Dörthe Brüggmann: Resources; Validation; Visualization; Writing – review & editing; David A. Groneberg: Project administration; Resources; Software; Writing – review & editing.

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Ethical statement

Neither humans nor animals were involved in this study and neither human nor animal tissue was used. Therefore, no ethical approval was required to perform the analyses.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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